REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised so as to define the invention with additional clarity.

Support for the revision of claim 20 to recite doses of activin up to 5ng per centimeter of wound or fibrotic disorder to improve the macroscopic appearance of wounds can be found in the experimental results reported in the specification (see, for example, the final paragraph of page 14). These results also indicate that the ability to reduce macroscopic scarring decreases when the amount of activin administered is increased. The recitation of the administration of doses per centimeter of wound or fibrosis finds support in the study set out in the experimental results which makes it clear that the recited doses of activin were each administered to a 1 cm wound (see, for example, page 11, second paragraph under "Materials and Methods"). It would be clear to an artisan that these doses should be "scaled up" when treating longer wounds. Hence, one skilled in the art would recognize that it is the administration of the specified amount of activin per centimeter length of the wound that is important in achieving the biological effect required (i.e., a reduction in scarring).

Claim 23 has been revised to properly depend from claim 20. Claim 31 as presented does not include the term "similar" to which the Examiner objects and claim 32 has been revised so as to make it clear that the wound or fibrotic disorder is a corneal wound. Claim 32 has been further revised to delete the reference to intradermal injection - that route of administration is recited in new claim 34. Claim 33 has been revised so as to simplify the language used. New claim 35 finds support, for example, in the "Conclusions" on page 14. Claim 21 has been

cancelled without prejudice and the dependency of claims 25-27 revised accordingly. Claims 29 and 30 have also been cancelled without prejudice.

Further experiments have been conducted in order to compare the effect on scarring of the doses of activin of the present invention and those considered by Mitrani. Details of the study undertaken, and the results obtained, are set out in the attached Appendix.

Claims 20, 21, 25 and 29-33 stand rejected under 35 USC 102(e) as allegedly being anticipated by Mitrani. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Claim 20 as now presented refers to a particular amount of activin to be administered per centimeter of wound or fibrotic disorder, in order to macroscopically reduce scarring. The experimental results set out in the subject specification indicate that macroscopic effects on scarring are limited to this particular range of doses . The recited doses are much lower than those considered in Mitrani (as discussed below), and give rise to beneficial biological effects that are not found on administration of higher doses.

At the outset, attention is directed to the fact that the doses referred to in claim 20 are defined in a different manner to those described in Mitrani. Claim 20 as now presented refers to the amount of the active agent (activin) administered to a given length of a wound or fibrotic disorder, whereas the cited art refers to amounts of the active agent that can be administered per unit body mass of a recipient. This is not an arbitrary difference in definition. As discussed further below, Applicants have found that doses defined in the manner referred to in claim 20 are more relevant in the context of wound healing than doses of the sort described in Mitrani.

Therapeutic manipulation of the healing process in order to reduce scarring is typically achieved by local, acute administration of therapeutic agents at the required site of action in the

skin. These administrations influence the milieu surrounding the cells at the site of the wound or fibrosis but generally do not give rise to significant quantities of the agent in the circulation. Local administration in this manner reduces the systemic availability of the therapeutic agent (thus helping to reduce unwanted side effects), and reduces "clearance" of the therapeutic agent by the systemic metabolism.

When defining the amount of a therapeutic agent to be used to influence the healing response it is, therefore, important to set the limits in terms of the amount of the agent to be provided to an area where it is to have its effect. A definition of this sort will most accurately reflect the influence that is achieved on the local healing environment.

References to an amount of an active agent per unit body mass (of the sort found in Mitrani) are generally more relevant in cases where it is necessary to establish upper doses of a systemically administered agent that will be tolerated by a patient. Since the ability of a patient to centrally metabolize a therapeutic compound roughly correlates with the patient's mass (liver size tending to increase as body size increases), such calculations can be useful in avoiding the risk of over-dosing.

This is of relevance since the Examiner has previously objected that "there has been no direct comparison of the application of the doses of exogenous activin suggested by Mitrani with the doses of exogenous activin taught in the examples of the present application". In light of the comments above, it will be appreciated that the doses recited in the present claims and those disclosed in Mitrani cannot be compared on an entirely "like-for-like" basis. However, a useful comparison can still be performed, and the Applicants have endeavored to provide this type of comparison in the further experimental study described in the attached Appendix.

As reported on page 14 of the subject specification (in the first sentence of the final paragraph), experimental wounds treated with either 2.5ng or 5ng doses of activin gave rise to scars that were macroscopically better than the corresponding controls. The ability to beneficially reduce scarring is lost as the amount of activin administered increases, as shown by the fact that wounds treated with 10ng doses of activin did not show the same improvement in scarring. Claim 20 has been amended to more accurately reflect this finding, by specifying the dose of activin to be administered per unit length of a site in which healing with reduced scarring to be promoted.

It is important to note that Mitrani contains no data to illustrate the suggestion that activin can be used to control tissue repair. Accordingly, there are no working examples of a suitable dose that one skilled in the art could follow. It is only with the benefit of hindsight that it could even be suggested that Mitrani encompasses the doses of activin found by Applicants to reduce scarring. Applicants submit, however, that no such teaching is found in Mitrani.

The doses of activin considered in Mitrani are defined with reference to the amount of activin administered per kilogram of body weight, and not with reference to amount per unit length of the site to be treated (as per the claims as now presented). As pointed out above, it is not possible to directly compare the doses considered in the prior art to those recited in the amended claims. However, the doses considered by Mitrani appear to be generally much higher than those that Applicants have found to be effective to reduce scarring.

The circumstance in which the higher doses considered in Mitrani may most closely be made to approximate those considered in the instant claims would occur if a patient with a relatively low body weight were treated with the lowest dose disclosed in Mitrani (thus giving rise to a low total dose of activin administered), while at the same time possessing relatively long

wounds requiring treatment (meaning that the low total amount of activin was provided in respect of a long length of wound).

The lowest dose of activin considered in Mitrani is 0.001mg/kg (i.e., 1000ng activin/kg body weight). The average female human is lighter than a male, and has a body weight of approximately 70kg. Thus, an average female human given the lowest dose considered in Mitrani would receive a total of 70,000ng of activin.

The longest wounds that will generally be treated in a human patient to reduce scarring are those associated with breast reduction or augmentation. These may be up to about 35cm long. Thus, in the case of a female patient undergoing bilateral breast reduction, the total wound length to be treated might be up to 70cm.

Based on these calculations, it can be seen that, even in relatively extreme circumstances (lowest suggested dose, light patient, very large wounds) conversion of the lowest dose considered in Mitrani to the format of "amount of activin/centimetre wound length" would call for administration of 70,000ng of activin to a patient with 70cm of wounds, a dose of 1000ng of activin per centimetre of wound to be treated.

In the light of these calculations, Applicants have investigated the effects of exogenous administration of activin at a dose of 1000ng/cm of wound, in order that this administration might be compared with the doses recited in the amended claims. As shown in the attached Appendix, Applicants have found a dose of 1000ng activin/cm of wound to be treated does not give rise to the reduction in scarring that is found when using the much lower doses recited in the amended claim.

Accordingly, Applicants submit that Mitrani does not disclose the use of activin in an amount "sufficient to promote said healing so that said healing with reduced scarring is

promoted". In contrast, the subject application as filed, and the claim as now presented, clearly identify such therapeutically effective amounts.

It is noted that column 16 of Mitrani also discloses "activin preparations containing 3-300ng of activin per gram preparation". However, Mitrani provides no guidance as to how much of any of these preparations should be used when attempting to control tissue repair. In the instant application, Applicants teach that restricting the amount of activin administered to low doses within a relatively narrow dosage band is essential to achieving anti-scarring activity. Since Mitrani lacks any direction to the skilled person that would lead them to apply the preparations disclosed in a manner such that an anti-scarring amount is provided, it is respectfully submitted that Mitrani cannot be considered to disclose (inherently or otherwise) an amount of activin sufficient to promote healing with reduced scarring.

In view of the above, reconsideration is requested.

Claims 20, 21, 25 and 29-31 stand rejected as allegedly being anticipated by De Kretser. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

As set out above, in relation to Mitrani, the claimed invention results from Applicants' identification of a particular narrow band of doses of activin that are able to reduce scarring at a site where activin has been administered. The experimental data included in the application as filed, and in the further illustrative results set forth in the attached Appendix, clearly illustrate that the ability to improve the macroscopic appearance of scars is not found across all doses but is, in fact, limited to the specific doses referred to in the claims.

The disclosure of De Kretser provides no teaching of specific doses of activin that can be used. Certainly, this document does not disclose the doses that Applicants have found to be important in achieving a reduction in scarring.

In the sentence spanning columns 12 and 13, De Kretser refers to the use of "a tissue regeneration promoting amount of activin" for administration to a host. No guidance is provided as to how much activin may provide such a "tissue regeneration-promoting amount".

It is worth noting that the scarring process addressed by the instant application is a reparative, rather than regenerative, process. The scar that arises after injury is an artefact of this repair, and may thus be readily distinguished from the original unwounded tissue. This is quite distinct from regenerative processes (of the sort considered in De Kretser) that are intended to give rise to a replacement tissue that cannot be distinguished from the unwounded tissue that existed before wounding.

Given that repair and regeneration are very different biological processes, even were the artisan able to deduce an amount of activin capable of promoting tissue regeneration, there can be no certainty that this amount would have any beneficial effects on the repair process (i.e., by reducing scarring in the manner required by the present claims). Since De Kretser provides no indication as to the amount of activin that is to be used to promote tissue regeneration, and since Applicants have found that the effects of activin on scarring are highly dose-dependent, it is respectfully submitted that there can be no good reason for suggesting that these anti-scarring amounts of activin are inherently disclosed by De Kretser.

In view of the above, reconsideration is requested.

Claims 20, 21, 26 and 27 stand rejected under 35 USC 103 as allegedly being obvious over Mitrani or De Kretser in view of Ferguson. Withdrawal of both of these rejections is submitted to be in order for the reasons that follow.

The Examiner has previously suggested that those claims found to be novel in the light of Mitrani or De Kretser would have been obvious when the teachings of either of these documents were combined with the teaching of Ferguson *et al.* Applicants respectfully disagree.

As set out above, neither Mitrani nor De Kretser disclose the importance of limiting the amount of activin that is applied to a body site in order for scarring to be reduced. Applicants have found that macroscopic scarring is reduced by the provision of up to 5ng of activin per centimeter of a body site at which scarring is to be reduced.

The teachings of Ferguson relate to sugar phosphates, and, in particular mannose-6-phosphate. These sugar derivatives are chemically and biologically distinct from the growth factor activin that is recited in the instant claims. Furthermore, the compounds disclosed in Ferguson demonstrate a profile of activity that is quite different from the profile of anti-scarring activity identified for activin. Ferguson shows that mannose-6-phosphate has its best activity at 20mM or 50mM, and that "[l]ower concentrations gave little effect, presumably through inadequate dosage" (page 9, first paragraph).

By way of contrast, the doses of activin shown by Applicants to be most effective, 2.5ng and 5ng corresponding to 96 fM and 192 fM, respectively, are far lower than the doses of mannose-6-phosphate considered in Ferguson. Furthermore, the data provided in the instant application show that the lower doses of activin used are the most effective at producing an anti-scarring effect.

Accordingly, Ferguson could not have cured the deficiencies of Mitrani and/or De Kretser, and indeed would have taught away from the subject matter of the claims as now presented. The skilled person, on considering the teaching of Ferguson, would not have been

motivated to use the very low doses of activin required in the present claims but, instead, would have believed that higher doses would be preferable for the reduction of scarring.

Reconsideration and withdrawal of the rejections are requested.

Claim 32 stands rejected under 35 USC 112, first paragraph. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of that claim. Reconsideration is requested.

Claims 22 and 31 stand rejected under 35 USC 112, second paragraph. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of those claims. Reconsideration is requested.

Claims 32 stands rejected under 35 USC 103 as allegedly being obvious over Mitrani in view of Hayashi, or Mitrani in view of Ferguson. Both rejections are traversed.

Claim 32 depends from claim 20 and thus the arguments presented above regarding the fundamental failings of Mitrani are equally applicable here. Neither Ferguson nor Hayashi provide any teaching that would have cured this deficiency. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: Mary J. Wilson

Mary J. Wilson
Reg. No. 32,955

MJW:tat
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

Experimental study comparing macroscopic effect on scarring of administration of different doses of activin

1 Summary

In the currently outstanding Office Action, the Examiner had objected that "there has been no direct comparison of the application of the doses of exogenous activin suggested by Mitrani with the doses of exogenous activin taught in the examples of the present application". The following experimental study was undertaken to address the Examiner's objections in this respect.

Although a "direct" comparison between the "weight/kg" doses considered in Mitrani and the "weight/cm" doses considered in the present application is not possible, the best available comparison has now been directly made. This comparison indicates that the macroscopic reduction in scarring seen on application of up to 5ng of activin per centimetre of wound is not achieved when 1000ng of activin is provided to a centimetre of wound.

2 Background

The inventors undertook a study to compare the effects of administration of activin and doses considered in the claims with administration of activin at doses considered in the prior art by Mitrani. Doses in accordance with the claims were represented by administration of 2.5ng/cm of wound or 5ng/cm of wound, while the prior art dose (calculated as the lowest possible dose per cm of wound, in the manner discussed in the accompanying letter) was represented by administration of 1000ng of activin per cm of wound.

3 Methods

Activin (R&D systems, batch number BNV17) was dissolved in phosphate buffered saline (PBS) to produce injectable solutions described further below.

Male Sprague Dawley rats (200-250g) were anaesthetised, partially shaved and marked with sites for formation of 1cm experimental wounds (two wounds per animal, each 1cm wound being formed 5cm from the base of the skull and 1cm from the mid line of the animal). Sites where wounds were to be formed were provided with either a controlled injection (100µl PBS) or a 100µl injection of a medicament providing 2.5ng activin, 5ng activin or 1000ng activin. These injections gave rise to a raised bleb, which was then immediately incised to form the 1cm experimental wound. All wounds were then re-injected one day post-wounding with the appropriate treatment (control or activin doses as discussed above) via injection of 50µl to each of the two margins of the 1cm wound.

The macroscopic appearance of scars produced on healing of the experimental wounds was assessed 70 days after wounding. The appearance of the scars was rated using a visual analogue scale (VAS) in which 0 represents unwounded skin, and 10 severe pathological scarring. A reduction in scarring thus gives rise to treated wounds having a lower VAS score than controls, while an increase in scarring gives rise to treated wounds having a higher VAS score than controls.

4 Results

Control wounds (to which only the diluent PBS was administered) gave rise to scars with a mean macroscopic VAS score of 5.8.

Treatment of wounds with activin at a dose of 2.5ng per centimetre gave rise to scars with a mean score of 4.1 on the macroscopic VAS. This value (which is lower than the score for the control wounds) represents a 30% reduction in macroscopic scarring.

Treatment of wounds with activin at a dose of 5ng per centimetre gave rise to scars with a mean score of 4.5 on the macroscopic VAS. This value represents a 22.5% reduction in macroscopic scarring as compared to control wounds.

Wounds treated with activin at a dose of 1000ng per centimetre gave rise to scars with a higher mean macroscopic VAS score of 6.1. Since this value is higher than the controls, it can be seen that administration of activin in accordance with the teachings of the prior art served to exacerbate, rather than reduce, scarring.

These results are shown graphically in the bar chart below.